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REMARKS

The Office Action has been carefully reviewed. No claim is allowed. Claims 1, 16, 19, 21, 23, 44, and 55-58 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 24, 26-34, 45, and 54, directed to pharmaceutical and vaccine compositions for the treatment of cancer, have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. While applicants do not concede to the examiner's position, this rejection is made moot by the cancellation of the rejected claims without prejudice to the filing of a continuation application thereon in order to advance prosecution.

Claims 1, 16, 19-21, 23, 44, and 55-58 have been rejected under 35 U.S.C. §101 because the claimed invention is directed to non-statutory subject matter. Claims 1, 16, 19, 21, 23, 44, and 55-58 are now amended as suggested by the examiner, thereby obviating this rejection.

Claims 1, 19-21, 23, 24, 26-34, 44, 45, 53, 54, and 58 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The examiner states that the specification at page 38, third paragraph, states that only human Lactadherin (BA-46) was known in the art. The examiner holds however that the specification does not teach the chemical structure(s) of any Lactadherin other than saying that a human Lactadherin (BA-46) sequence is known in the art. It is the examiner's position that any other Lactadherin sequence besides human Lactadherin sequence had not been known in the art before the effective filing date of the instant application.

This rejection is now obviated by the amendment of claims 1, 19, and 58 to recite for "human" Lactadherin (BA-46). The sequence of human Lactadherin is presented in the Larocca et al., Cancer Res. 15:4994-4998 (1991), paper cited in the specification at page 38, lines 22-24, as reference 68, a copy of which is attached hereto. Also attached hereto is a printout from the NCBI database for the accession number 1589428 disclosed in the specification at page 39, line 18 (Table 7). It is clear from this printout that the human Lactadherin (BA-46) sequence was publicly available in a sequence database as of at least November 4, 1996. Accordingly, the human Lactadherin (BA-46) sequence was available in the art at the time the invention was made and the amendments to the claims obviate this rejection.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By _____
ALLEN C. YUN
Registration No. 37,971

ACY:pp
624 Ninth Street, N.W.
Washington, D.C. 20001
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\Y\YEDA\Eisenbach3\PTO\amd OA 2-20-04.doc

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Advances in Brief

A M_r 46,000 Human Milk Fat Globule Protein That Is Highly Expressed in Human Breast Tumors Contains Factor VIII-like Domains[1]

David Larocca,[2] Jerry A. Peterson, Ramon Urrea, Jon Kuniyoshi, Antonio M. Bistrain, and Roberto L. Ceriani

John Muir Cancer and Aging Research Institute, Walnut Creek, California 94596

Abstract

The human milk fat globule has proved to be a good source of antigenic material for production of antibodies against surface components of breast epithelial cells. Monoclonal antibodies against one of the major components of the human milk fat globule, which identify a glycoprotein with an apparent molecular weight of 46,000, have been found to be useful for both breast cancer diagnosis and therapy. In order to characterize this M_r 46,000 glycoprotein, specific monoclonal antibodies were used to select complementary DNAs from a λgt11 expression library from lactating breast. The largest complementary DNA insert (BA46-1) was 1270 base pairs and encoded 217 amino acids. A single 2.2-kilobase RNA was specifically detected in a variety of carcinoma cell lines, using this complementary DNA probe, and it was overexpressed in some carcinoma lines. The mRNA levels correlated with the level of expression of the antigen in these cell lines as detected by Western blot analysis. Sequence analysis revealed strong homology of the M_r 46,000 glycoprotein with serum factors VIII and V, in the region implicated in phospholipid binding.

Introduction

HMFG[3] proteins have been the focus of extensive basic, preclinical, and clinical studies because of their importance as immunogens for development of antibodies against surface antigens of breast epithelial cells (1). Antibodies raised against HMFG proteins have been used for developing breast cancer imaging and immunotherapy (2, 3) as well as immunodiagnostics (4) and histopathology (5). The high-molecular-weight breast mucin component of HMFG has been the focus of much attention in this regard; however, the lower-molecular-weight components, in particular the M_r 46,000 component, also have shown considerable promise as tumor markers and targets for therapy. Early work using both polyclonal and monoclonal antibodies that specifically bound the M_r 46,000 component of HMFG showed the presence of M_r 46,000 antigen in the sera of patients with breast tumor metastasis but not in a melanoma patient or in a normal healthy female control (4). Also, the M_r 46,000 component of HMFG has been shown to participate in circulating immune complexes in breast cancer patients (6). An increase in the circulating M_r 46,000 antigen was found to be associated with limited tumor burden, but it decreased in advanced disease, presumably due to the formation of immune complexes (6). The importance of the M_r 46,000 antigen for therapy is suggested by preclinical studies that showed that ^{131}I-conjugated anti-M_r 46,000 monoclonal antibody, Mc3, effectively inhibited the growth of human tumors in nude mice for up to 30 days when used alone or in a cocktail of ^{131}I-labeled anti-HMFG antibodies (3). Recent efforts have focused on characterizing the structure of the genes encoding the breast mucin and smaller HMFG antigens. Several groups have cloned and sequenced the cDNA encoding the high-molecular-weight mucin component of HMFG (7–9). It consists of a highly immunogenic 20-amino acid repeat and flanking unique sequences. There is evidence that the breast mucin forms a complex with the M_r 70,000 HMFG component involving disulfide linkages (10). A partial cDNA that encodes an antigenic region of the M_r 70,000 component has recently been characterized (11). This sequence appears to differ from another M_r 70,000 component, termed butyrophylin, that is found in milk fat globules from different species and which has recently been cloned and sequenced from cows (12). A M_r 67,000 component from mouse milk fat globule has also been cloned and sequenced (13). The mouse protein is distinct from butyrophylin (12) but shares extensive homology with blood clotting factors VIII and V and contains epidermal growth factor-like repeat sequences. The function of these proteins remains unknown. Here we describe the cDNA cloning and characterization of a potential target antigen and tumor marker for breast cancer treatment and diagnosis, the M_r 46,000 component of human milk fat globule. Surprisingly, it appears to represent a truncated version of the mouse M_r 67,000 component having the factor VIII-like sequences. The factor VIII homology is in the C1C2 region that is thought to be involved in phospholipid binding. This gene is highly expressed in certain human tumor cell lines, and its protein is found primarily in the detergent-soluble cell fraction.

Materials and Methods

Immunoscreening the λgt11 cDNA Library. A human breast cDNA Library was purchased from Clontech (Palo Alto, CA). The library was prepared from RNA extracted from adult breast tissue excised during mastectomy, during the 8th month of pregnancy, showing well-differentiated tissue and lactational competence. The oligodeoxythymidine-primed cDNA from this tissue was inserted into the *Eco*RI site of λgt11. Plating and screening of the library with MoAbs were done as described previously (11). The library was screened with a cocktail of MoAbs Mc3, Mc8, Mc15, and Mc16 (14), all of which bind the M_r 46,000 component of human milk fat globule.

Blot Analysis. Cell lines were grown to late log phase, and total cell RNA was prepared by the guanidinium/CsCl gradient method (15). RNA was denatured, electrophoresed, and blotted using standard protocols (15) and was bound to nylon (Biodyne) filters using UV irradiation. Single-stranded RNA probes were made *in vitro*, using SP6 and T7 RNA polymerase according to the manufacturer's instructions (Promega), and labeled by incorporation of [^{32}P]UTP at 800 Ci/mmol (Amersham). Hybridization of RNA probes to RNA blots was carried out at 65°C. The highest-stringency wash was at 70°C (0.1 × standard saline citrate [0.15 M sodium chloride, 0.015 M sodium citrate], 0.1% sodium dodecyl sulfate). Blots were exposed to X-ray film (Kodak X-AR) at −80°C with intensifying screens.

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[2] To whom requests for reprints should be addressed, at John Muir Cancer and Aging Research Institute, 2055 North Broadway, Walnut Creek, CA 94596.

[3] The abbreviations used are: HMFG, human milk fat globule; MoAb, monoclonal antibody; cDNA, complementary DNA.

DNA Sequencing. Large-scale bacteriophage DNA preparations were made from phage lysates, and the *Eco*RI-digested cDNA insert was subcloned into pGEM3 (Promega, Madison, WI) according to standard protocols (15). Dideoxynucleotide-based sequencing of the insert in pGEM3 was done with a modified T7 DNA polymerase (Sequenase) directly on the plasmid DNA using T7 or SP6 promoter sequence primers (Promega) according to the manufacturer's protocol (USB, Cleveland, OH). The sequence was confirmed by sequencing both strands of the insert.

Western Blotting. Cell lysates were fractionated into aqueous and detergent-soluble fractions by the method of Bordier (16). This method takes advantage of the fact that Triton X-114 remains in solution at 0°C but separates into phases above 20°C. Briefly, total cell protein was solubilized in 0.5% Triton X-114 in Tris-buffered saline, pH 7.4, at 0°C. The solution temperature was raised to 30°C, and the detergent was pelleted through a sucrose cushion to separate the detergent and aqueous phases. Aliquots of 25 mg (detergent fraction) and 50 mg (aqueous) were loaded onto 4–15% gradient gels for sodium dodecyl sulfate-polyacrylamide gel electrophoresis. The proteins were electrophoresed and blotted electrophoretically. The blot was processed by incubating with 1 μg/ml Mc16 in 10 mM Tris (pH 7.5), 250 mM NaCl, and 0.05% Triton X-100 overnight at room temperature, washing, incubating 3 h with horseradish peroxidase-conjugated goat anti-mouse antibody, and the reactive bands were visualized using diaminobenzidine substrate.

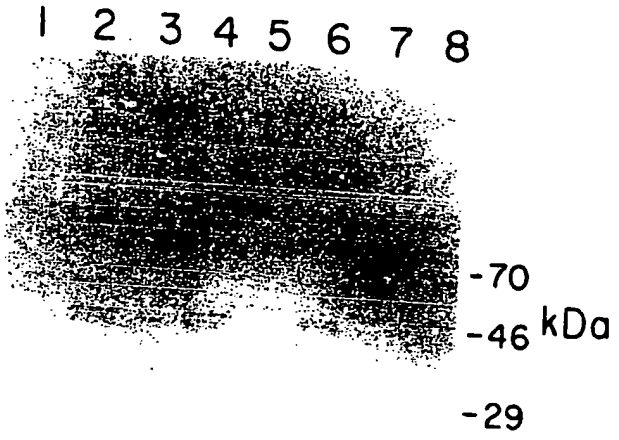

Fig. 2. Western blot analysis of BA46 protein in human cell lines. Samples were fractionated and the blot prepared and processed as described in "Materials and Methods." *Lanes 1, 3, 5,* and *7*, aqueous fractions of cell lines A549, HS578T, ELL-G, and Raji, respectively; *Lanes 2, 4, 6,* and *8*, detergent-soluble fractions of A549, HS578T, ELL-G, and Raji, respectively. The blot was incubated overnight at room temperature with 1 μg/ml Mc16 in 10 mM Tris (pH 7.5), 250 mM NaCl, and 0.05% Triton X-100.

Results and Discussion

We selected 15 positive plaques in a screen of about 1×10^6 plaques from a λgt11 lactating breast cDNA library. The largest cDNA, BA46-1, was 1270 base pairs long. A series of positive λgt11 clones were used to lysogenize Y1089, and the resulting fusion protein containing induced cell extracts was analyzed by dot blot analysis for reactivity with each of the MoAbs contained in the screening cocktail. We found that Mc8, Mc15, and Mc16 bound to all the positive λgt11 lysogen extracts but not to control λgt11 extract (not shown). Mc3, however, did not bind any of the lysates, indicating that its epitope requires glycosylation or secondary structure or is not present on the isolated cDNA clones or in the library.

Single-stranded RNA probes representing each strand of the BA46-1 cDNA insert were prepared by subcloning into Gem3 and transcribing *in vitro* with T7 or SP6 polymerase. We analyzed several carcinoma cell lines including 7 breast lines and a lymphoid cell line for BA46-1-specific RNA. As shown in Fig. 1, we detected a single 2.2-kilobase RNA in most carcinoma cell lines tested when using the antisense strand as a probe. This RNA is also detectable in the remaining carcinoma lines and Raji but at much lower levels requiring longer exposures than shown in Fig. 1. There was considerable variation in the observed expression levels of the 2.2-kilobase RNA that we detected in the carcinoma cell lines. The lung (A549), ovary (SKOV3), and two breast cell lines (Ell-G and HS578T) accumulated much more of this transcript than the other carcinoma cell lines. Overexpression of certain genes, such as Her2/*neu* (17), in breast and other carcinomas has been correlated with prognosis. It will be of interest to determine whether overexpression of the M_r 46,000 protein in carcinomas correlates with outcome of disease.

Although the antibodies used to select the cDNAs were specific to breast, the expression of the 2.2-kilobase RNA and its M_r 46,000 protein product occurs in several different carcinoma cell lines. The lack of breast specificity may be due to a deregulation of this gene in carcinomas but not in normal tissue. Alternatively, normal epithelial tissue may express the M_r 46,000 protein but process it in a way that blocks the epitopes

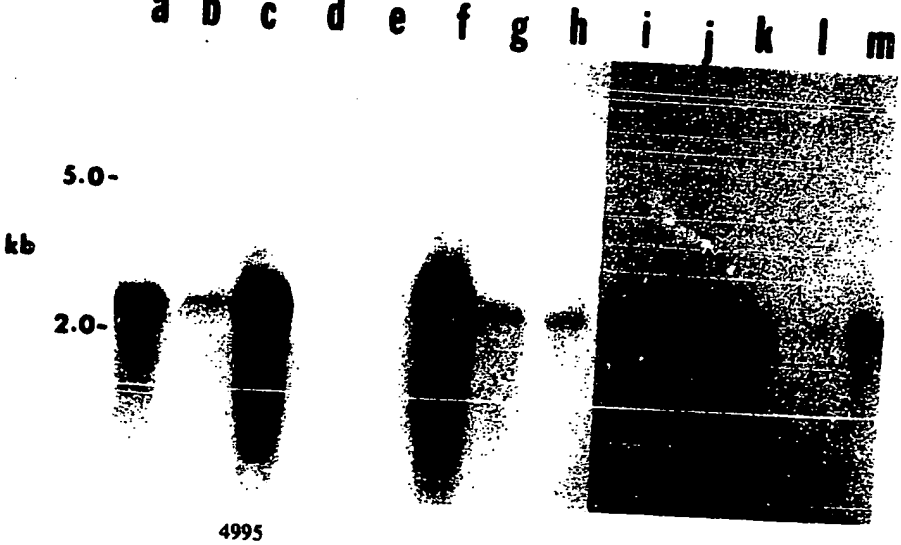

Fig. 1. Expression of BA46-1 specific mRNA in human carcinoma cell lines. Total RNA (20 μg/lane) was run on a 1.4% agarose gel, blotted, and hybridized to ^{32}P-labeled RNA generated from the BA46-1 cDNA clone. *Lane a*, A549 (lung); *Lane b*, BT20 (breast); *Lane c*, ELL-G (breast); *Lane d*, Raji (lymphoid); *Lane e*, SKBR3 (breast); *Lane f*, SKOV3 (ovary); *Lane g*, MDA-MB-361 (breast); *Lane h*, MDA-MB-331 (breast); *Lane i*, HeLa (cervix); *Lane j*, HS578T (breast); *Lane k*, HT29 (colon); *Lane l*, PanCI (pancreas); *Lane m*, MCF-7 (breast). Exposure was 16 h with an intensifying screen.

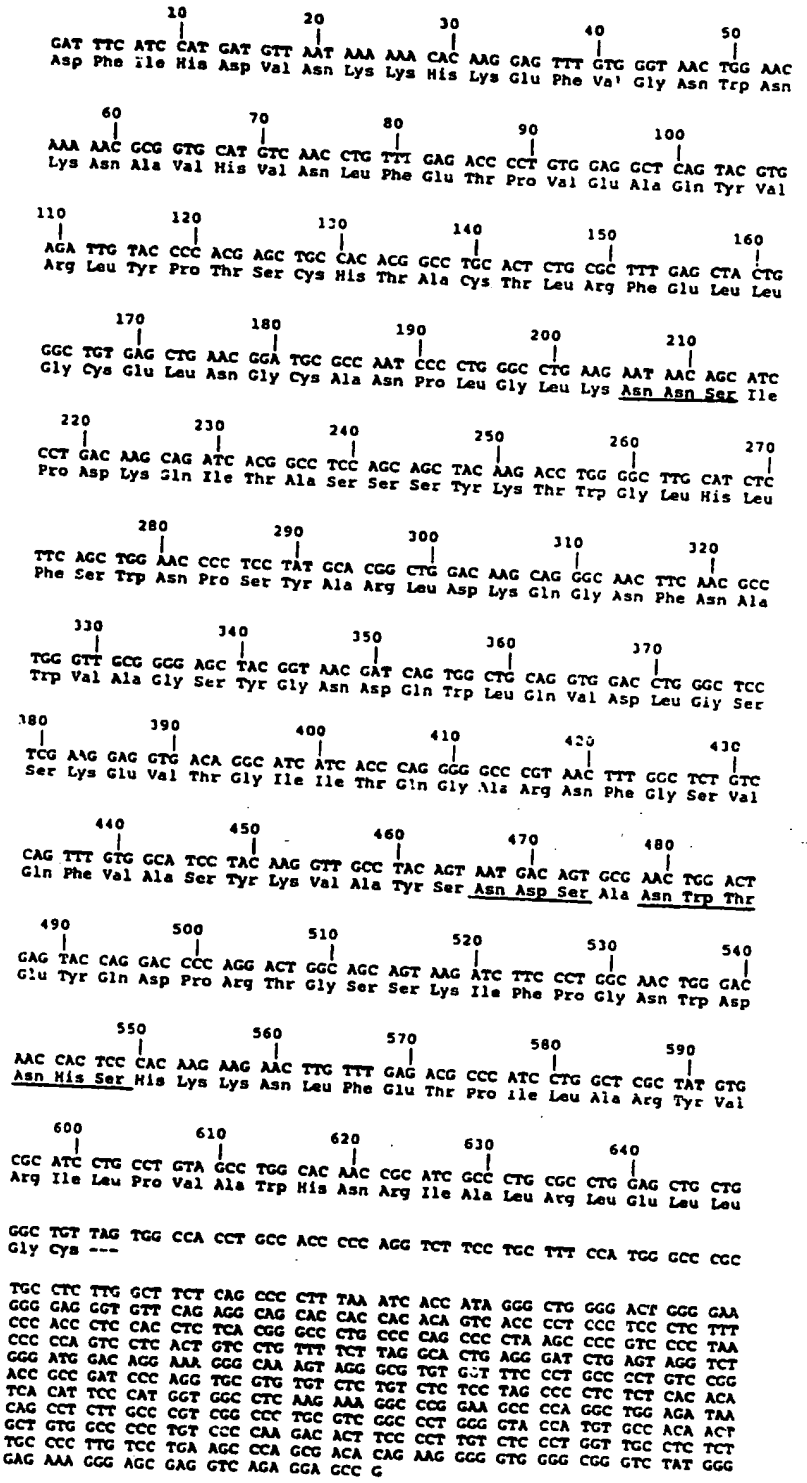

Fig. 3. DNA sequence and derived amino acid sequence of BA46-1 cDNA. *Underlines*, potential *N*-linked glycosylation sites.

that are exposed in the breast cell version of the protein by, for example, alterations in glycosylation. The high-molecular-weight mucin-like protein of HMFG is also expressed in non-breast carcinomas. For example, alternative processing in the pancreas leads to the exposure of antigenic sites different from those in the breast (18).

We initially investigated the presence of BA46 in various human tumor cell lines by Western blot analysis of total cell protein. However, the amount of BA46 present was marginally within the limits of our detection. We therefore fractionated the cells into detergent-soluble and aqueous fractions using Triton X-114, as described by Bordier (16). By this method, integral membrane proteins are partitioned into the Triton X-114 phase. The Western blot shown in Fig 2 shows that the

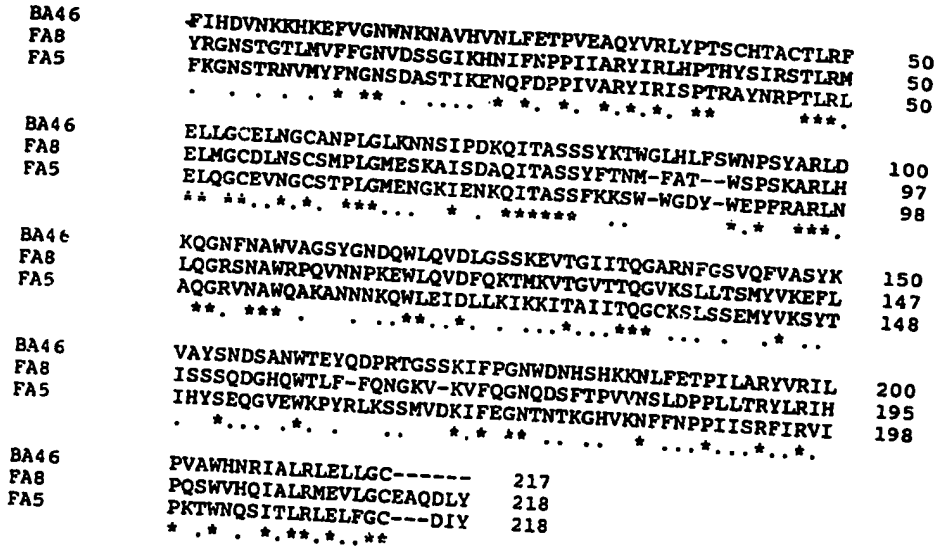

Fig. 4. Comparison of the derived BA46-1 amino acid sequence with the COOH-terminal sequence of human serum factors V and VIII, using the Clustal program of PCGene (Intelligenetics, Palo Alto, CA). *, perfectly conserved; ·, well conserved.

BA46 is detected only in the detergent-soluble fraction and that it is detected in those cell lines that overexpress the BA46 mRNA relative to Raji and other cell lines tested (not shown). Thus, there was a good correlation between mRNA synthesis and BA46 protein accumulation in these cell lines.

The nucleotide and deduced amino acid sequences of BA46-1 cDNA are shown in Fig. 3. The partial sequence is 217 amino acids long, having a theoretical molecular weight of 25,000, representing the COOH terminus of the complete protein. There are 4 potential sites for *N*-linked glycosylation. The sequence is asparagine and leucine rich. A comparison of the nucleotide sequence to the EMBL database using FSTNSCAN (PCGENE) revealed extended homology with human serum factor V, VIII, and protein C. The deduced protein sequence, however, shares identity only with factors V and VIII (see Fig. 4) but not with protein C since the homology at the nucleotide level is in an intervening sequence of protein C. There is 43% identity of BA46 with factor V and 38% with factor VIII. The regions of factors V and VIII shown in Fig. 4 share 47% identity (19). The mouse M_r 67,000 protein MFG-E8 (13) COOH terminus is 60% identical to the BA46 partial sequence presented here.

Analysis of the deduced amino acid sequence of the M_r 46,000 protein is consistent with that of a glycosylated protein. The function of this protein is unknown. The homology with clotting factors is in the C1, C2 region of the light chain of factor VIII. Arai *et al.* (20) have shown that human antibodies (from hemophiliacs treated with factor VIII) that bind this region of the light chain inhibit factor VIII by preventing the interaction of factor VIII with phospholipid. Since this region has been implicated in phospholipid binding it is likely that it serves a similar role in the M_r 46,000 glycoprotein. The appearance of a shared domain in otherwise different proteins might be due to exon shuffling. The COOH terminus could serve as a novel "anchor" sequence for the M_r 46,000 glycoprotein. Alternatively, it could be involved in the assembly of the mucin complex at the plasma membrane surface.

We find that BA46 is partitioned almost exclusively in the detergent-soluble fraction. However, there is no transmembrane domain in this sequence. Therefore, either this protein is anchored by an NH_2-terminal signal sequence, or the anchoring or association with membrane is via some alternative means like its association with phospholipid. Many apical proteins are shuttled to the membrane surface via covalent linkages to phospholipid. However, in this case the association may be a weaker noncovalent binding as suggested by the similarity of BA46 with the phospholipid binding domain of factor VIII. An association via disulfide linkages to other integral membrane proteins (perhaps the mucin or BA70) cannot be ruled out. There are 5 cysteines in the deduced amino acid sequence we have obtained from cDNA cloning and sequencing.

In addition to studying the structure of the M_r 46,000 protein, the full-length cloning and expression of the cloned M_r 46,000 protein gene in bacterial and eukaryotic cells will be useful for assessing function such as phospholipid binding, for further studies of circulating human epithelial antigen in cancer patients, and for developing improved antibodies for targeting therapeutics and for tumor imaging.

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DEFINITION  breast epithelial BA46 antigen.
ACCESSION   2211263A
VERSION     2211263A  GI:1589428
DBSOURCE    prf: locus 2211263A;

            state: embryo;
            taxonomy: Mammalia.
KEYWORDS    Breast Epithelial BA46 Antigen; Human; cDNA Clone; Seq
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            Domain; Assocd with Breast Cancer.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (residues 1 to 387)
  AUTHORS   Couto,J.R., Taylor,M.R., Godwin,S.G., Ceriani,R.L. and
            Peterson,J.A.
  TITLE     Cloning and sequence analysis of human breast epithelial antigen
            BA46 reveals an RGD cell adhesion sequence presented on an
            epidermal growth factor-like domain
  JOURNAL   DNA Cell Biol. 15 (4), 281-286 (1996)
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